A Synopsis

SYNTHESIS OF SOME POTENTIALLY BIOACTIVE HETEROCYCLES

For

Partial fulfillment of Ph. D. Degree in Science

MODY UNIVERSITY
OF SCIENCE AND TECHNOLOGY
LAKSHMANGARH • RAJASTHAN
A LEADING WOMEN'S UNIVERSITY

Ms. Priyanka Khyaliya

SUPERVISOR
Dr. K. L. Ameta
Associate Professor

Department of Chemistry
College of Arts, Science and Humanities (CASH)
Mody University of Science and Technology (MUST)
Lakshmangarh, Sikar (Rajasthan – 332311) INDIA

CONTENTS

S.NO	TITLE
1	INTRODUCTION
2	OBJECTIVES
3	METHODOLOGY
4	IMPORTANCE OF PROPOSED INVESTIGATION
5	REVIEW OF WORK ALREADY DONE ON THE SUBJECT
6	REFERENCES

1. INTRODUCTION

Chalcones constitutes an important group of natural products showing different biological and pharmacological activities[1]. Chalcone have displayed an impressive array of biological importance. Chalcones are considered to be precursors of flavonoids, found as naturally-occurring compounds. They can also be synthesized in laboratory. Chalcones possess a broad spectrum of biological activities including antioxidative, antibacterial, anti fungal, antimitotic, anti-leishmanial, anti-invasive, antimalarial, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic and immunosuppressive and anti-tumor properties. They have received much importance in recent years because of their diverse biological activity and synthetic utility. Some chalcones have the ability to block voltage-dependent potassium channels. They have been recognized as interesting compounds with cytotoxic and tumor reducing properties. They are also used as an intermediate in the biosynthesis of flavonoids, which are widespread in plants with an array of biological activities. Chalcones are found to be versatile and convenient intermediates in the synthesis of a wide variety of heterocyclic compounds. The α,β-enone moiety of these molecule is a favorable unit for dipolar cycloaddition with numerous reagents providing pharmacologically interesting heterocyclic systems such as thiazines, pyrimidines, and pyrazoles.

Chalcones and their analogues are especially important starting materials or intermediates for the synthesis of naturally occurring flavonoids[2]. Chalcones are a group of plant-derived polyphenolic compounds that belong to the flavonoids family, and possess a wide variety of cytoprotective and modulatory functions. They are widespread components in all parts of the plants used as flower pigments and growth regulators. The present research work focuses the chalcones as basic platform to develop some novel heterocycles with potential bioactivity.

2. OBJECTIVES

- To synthesize chalcones and other substrates by using conventional / non-conventional methods.
- To explore the cyclization of chalcones and other substrates to heterocycles using suitable reagents by conventional / non-conventional methods of synthesis.
- Characterisation of synthesized compounds using analytical and spectral methods.

- To carry out possible clinical trials of synthesized compounds and correlate the structure activity relationship.

3. METHODOLOGY

Chalcones have been synthesized by two routes:

(1) Conventional route

(2) Non-conventional route

The non-conventional routes basically include Microwave irradiation,Water mediated, Ultrasonic and Photochemical process. The use of such non-conventional reaction condition has several advantages like shorter reaction time, increase yield, selectivity in reaction, easy of reaction work-up, eco-friendliness as compared to conventional route. Conversion of the synthesized chalcones into potentially bioactive heterocycles such as aurones, 1,5-benzothiazepines, 3,4-dihydroquinoxaline, oxazines, thiazines, pyrimidines, 1,3-dicarbonitrile derivatives etc. will be carried out using conventional as well as non-conventional protocols.

4. IMPORTANCE OF PROPOSED INVESTIGATIONS

Chalcones and their derivatives are reported to inhibit the growth of several pathogenic micro-organisms and fungi are also claimed to exhibit interesting therapeutic properties. The presence of enone system in the chalcone molecule along with substituted nuclei confers important biological activities. These compounds also show profound influence on the cardiovascular, cerebrovascular and neuromuscular systems.

Secondly, chalcones having an enone are important Michael acceptors and are involved in the synthesis of noval heterocycles. Heterocycles represent today one of the most dynamic and challenging areas of chemistry. In recent decade there have been explosions of activity in the chemistry of heterocyclic compounds because they contribute directly to the health of humans & animals. Endowed with this unique property heterocyclic compounds are well recognized for their multifaceted pharmacological, medicinal and biochemical behaviour.

Thirdly, chalcones and their derivatives have industrial applications as polymers, stabilizers, sweeteners, photosensitive materials, analytical reagents etc.

Finally, the envisaged work has been undertaken for improving the existing procedures for various reactions so that procedures would not only be environmentally desirable but also be economically viable & exploring newer vistas leading to innovation based on non-conventional (eg. microwave / water mediated / ultrasonic etc.) methods of organic synthesis. Therefore the topic of research of paramount importance. The proposed

work focuses the synthesis of chalcones and their cyclization using novel chemical methodologies to pyrimidines, benzoxazepines, pyrazolines, substituted thiourea derivatives *etc.*

5 . REVIEW OF WORK ALREADY DONE ON THE SUBJECTS

The chemistry of chalcones and their derivatives has been an interesting field of study for long time because they are useful intermediates in organic system[3]. A number of heterocyclic derivatives of chalcones have been reported. These include the chalcone derivatives of aziridine[4,5],coumarin[6], benzodiazepine[7,8], benzothiazepine[9,10] , benzofuran[11], large number of different biological activities. Some of chalcone and their derivatives show a profound influence on the cardiovascular, cerebrovascular, neurovascular systems. Heterocyclic derivatives shows a wide variety of biological activities such as antimicrobial[12], anti-inflammatory[13],antimalarial[14,15], antioxidant[16,17], antibercular [18,19], anticancer[22]etc. Some chalcone derivatives show herbicidal activity[23].

The synthetic utility of chalcones and their derivatives are also demonstrated as they undergo reactions with different reagents[24-30]eg. oxidizing, reducing esters, cyanides, amides, ketones, isocyanates amines, halogens, organometallic, photochemical, polarographic, biochemical & electrochemical. These heterocyclic compounds have also wide range of industrial applications [31-32] and are useful as biodegradable agrochemicals[33]. Some chalcones are also used as sweeteners, drugs[34], sunscreen agents, photoresists, photographic emulsions[35], optical properties[36] and sensing activities[37].

In the last few years these has been a growing interest in the use of microwave heating in organic synthesis because most of the thermally driven organic chemicals reactions can be accelerated by microwave. The use of such non-conventional reaction condition reveals advantages like short reaction time, increased yield, cleaner reaction,selectivity in reaction, ease of reaction work up, eco- friendliness as compared to conventional heating. Thus microwave assisted synthesis becomes a part of Green chemistry[38-41] as the developed procedures are both environmentally & economically acceptable.

In view of the above and our continued surge of interest in the fictionalization of various heterocyclic systems that have been explored for developing pharmaceutically important molecules by using conventional[42-43]& non conventional[44-47] synthetic routes, the current work proposal focuses the synthesis of chalcones and their cyclization using

novel chemical methodologies to pyrimidines, benzoxazepines, pyrazolines, substituted thiourea derivatives *etc.*

6. REFERENCES

1. Rojas, J.; Domınguez, J. N.; Charris, J. E.; Lobo, G.; Paya, M.; Ferra´ndiz, M. L. (2002). Synthesis and Inhibitory Activity of Dimethylamino-Chalcone Derivatives on the Induction of Nitric Oxide Synthase. *Eur. J. Med. Chem.*, *37*, 699.
2. Albert Lévai (2004), Synthesis of exocyclic α, β-unsaturated ketones. *Arkivoc*, *vii*, 15-33.
3. Dhar, D.N. (1981). 'The chemistry of chalcones and related compounds, Wiley-Inter Science, *New York.*
4. Sugihara, H., Daikai, K., Jin, X. L., Furuno, H. and Inanaga, J. (2002). *Tetrahedron Lett,* **43**, 15, 2735.
5. Nemoto, T., Ohshima, T. and Shibasaki, M. (2000). *Tetrahedron Lett*, **41**, 9569.
6. Joshi, U. K., Keldar, R. M. and Paradkar, M. V. (1983). *Indian J. Chem.*, **27B**, 1151.
7. Essaber, M., Baouid, A., Hasnaoui, A., Benharref, A. and Lavergne, J. P. (1998). *Synth Commun*, **28**, 4097.
8. Reddy, B. M. and Sreekanth, P. M. (2003). *Tetrahedron Lett*, **44**, 4447.
9. Sarroj, G. D., Chimirri, A. and Sarro, A. D. (1995). *Eur. J. Med. Chem.*, **130(12),** 925.
10. Sharma, K., Singh, G., Yadav, A. and Prakash, L. (1997). *Molecules*, **2(2),** 130.
11. Babu, V.H., Manna, S.K., Sneha, Srinivasan, K. K. & Bhat, G.V. (2004). *Indian J. Heterocyclic Chem.*, **13,** 253.
12. D'hooghe, M., Waterinckx, A. and De Kimpe, N. (2005). *J. Org. Chem.*, **70(1),** 227.
13. Dimmock, J. R., Elias, D.W., Beazely, M. A. & Kandepu, N.M. (1999). *Curr Med Chem.,* **6,** 1125.
14. Zhao, L. M., Jin, H. S., Sun, L. P., Piao, H. R. and Quan, Z. S. (2005). *Bioorg. Med. Chem. Lett,* **15,** 5027.
15. Yadav, H. L., Gupta, P., Pawar, P. S., Singour, P. K. and Patil, U. K. (2010). *Med. Chem. Res.,* **19,** 1.
16. Agarwal, Anu., Srivastava, Kumkum., Puri, S. K., Chauhan, M. S. Prem. (2005). Syn *Bioorg. Med. Chem.,***13,** 6226.
17. Wu, Xiang., Wilairat, Prapon., Go, Mei-Lin. (2002). *Bioorg. Med. Chem. Lett.,* **12(17),** 2299.
18. Vasil'ev, R. F., Kancheva, V. D., Fedorova, G. F., Batovska, D. I. and Trofimov, A. V. (2010). *Kinetics and Catalysis*, **51,** 507.
19. Sivakumar, P. M., Prabhakar, P. E.K. and Doble, M. (2010). *Med. Chem. Res.,* **19,** 1.
20. Sivakumar, P. M., Seenivasan, S, Prabu., Kumar, Vanaja., Double, Mukesh. (2007). *Bioorg. Med. Chem. Lett.*, **17,** 1695.
21. Lin, Yuh-Meei., Zhou, Yasheen., Flavin, Michael T., Zhou, Li-Ming., Nie, Weiguo., Chen, Fa-Ching. (2002). *Bioorg, Med. Chem.*, **10,** 2795.
22. Ilango, K., Valentina, P. and Saluja, G. (2010). *Bio. Chem. Sci.,* **1,** 354.

23. Satyanarayana, M., Priti, T., Tripathi, K., Srivastava, A. K. and Ram, P. (2004). *Bioorg. Med. Chem.*, **12,** 883.
24. Dwivedi, S., Misra, S. C. & Misra, R. A. (1996). *J. Indian Chem. Soc.*,**73,** 489.
25. Delcarmen, M., Barrio, G., Barrio. J. R., Novelli, A. & Leonard, N. (1973). *J. Am. Chem.*, **95,** 4891.
26. Metwally, M.A., Yusuf, M. Y., Tsmaeil, A. M. & Amer, F. A. (1985). *J. Indian Chem.*, **62,** 54.
27. Hafez, E. A., Elnagdi, M.H., Elagamey, A. A. & El-Taweel, M. A. F. (1987). *Heterocycles,* **26,** 903.
28. Ram, V. J.,Saxena, A. S.,Srivastava, S. and Chandra, S. (2000). *Bioorg. Med. Chem. Lett.*,**10,** 2159.
29. Ezio, B. and Piero, V. (2002). US, **6,** 423.
30. Gloria, L. A., Tawfeq, A. R. K. (2006). US, **8,**013.
31. Yang, J. X., Tao, X. T., Yuan, C. X., Yan, Y. X., Wang, L., Liu, Z., Ren, Y. and Jiang, M. H. (2005). *J. Am. Chem. Soc.*, **127,** 3278.
32. Bose, A. K., Banik, B. K., Lavlinskaia, N. ,Jayaraman, M. & Manhas, M. S. (1997). *Chemtech,* **18.**
33. Verma, R. S.(1999). *Green Chem.*, **1,** 43.
34. Galema, S. (1997). *Chem. Soc. Rev,* **26,** 233.
35. Caddick, S. (1995). *Tetrahedron,* **51,** 373.
36. Kothari, S., Singhal, M., Vijayvergiya, D., Vyas, R. & Verma, B. L. (2000). *J. Indian Chem.* Soc., **77,** 329.
37. Vijayvergiya, D., Kothari, S. & Verma, B. L. (2003). *Indian J. Heterocyclic Chem.*, **13,** 105.
38. Victory, Pedro., Barrell, Jose I., Vidal- Ferran, Anton., Seoane, Corlos. And Sota, Jose L. (1991). *J. Tetrahedron Letters,* **32,** 5375.
39. Ameta, K.L. & Verma, B. L. (2002). *J. Indian Chem.* Soc., **79,** 840.
40. Rao, S. S., Gahlot, U. S., Dulawat, S. S.,Vyas, R., Ameta, K. L. & Verma, B. L. (2003). *Afinidad,* **60(505),** 271.
41. Gahlot, U. S., Rao, S. S., Jhala, Y. S., Dulawat, S. S. & Verma, B. L.(2003). J. *Indian Heterocyclic Chem.*, **13,** 111.